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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,925	07/11/2001	Avi Ashkenazi	10466/86	1358

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HELLER EHRMAN WHITE & MCAULIFFE LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CO 94025-3506

EXAMINER	
HAMUD, FOZIA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,925	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Fozia M Hamud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/23/04; 7/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Receipt of Applicants' amendment and arguments, filed on 23 July 2004 is acknowledged. Claim 45 has been amended.

Status of Claims:

1b. Claims 1-44 have been cancelled. Claims 45-49 are pending and under consideration.

1c. Receipt of Applicant's declaration under 37 C.F.R §1.132, filed by Dr. Avi Ashkenazi and Dr. Paul Polakis filed on 18 June 2004 and 14 July 2004, respectively, is also acknowledged.

2. The following previous objection is withdrawn in light of Applicants' argument filed on 23 July:

2a. The rejection of claim 45 under 35 U.S.C. 112, second paragraph for reciting "....specifically binds...", is withdrawn, because Applicants' argument that the term "specifically binds", is art recognized to mean that the recited antibody binds to the recited polypeptide without significantly cross-reacting with other proteins, is found persuasive.

2. ***Priority:***

Applicants submit that the results of the gene amplification assay disclosed in parent applications PCT/US99/30095, filed 16 December 1999 (WO 00/37640), and 60/113,296 filed on 22 December 1998, provide a specific and substantial asserted utility for the antibodies claimed in the present application. Therefore, Applicants contend that the present application is entitled to the filing date of 22 December 1998.

This argument is not found persuasive. The claims of the instant invention are drawn to a method of diagnosing lung or colon cancer using an antibody that binds to the polypeptide of SEQ ID NO:263. However, said subject matter is not supported by the disclosure in the international application PCT/US99/30095, filed 16 December 1999 or in the provisional application No:60/113,296 filed on 22 December 1998, since these prior applications do not provide a specific and substantial asserted utility or a well established utility for the claimed invention. As was previously stated, the gene amplification assay described in the parent applications provide a specific and substantial asserted utility for the polynucleotide of SEQ ID NO:262, because the assay shows approximately 2-9 fold amplification of DNA sequences in lung and colon tumors compared to normal controls. However, the increased copy number of PRO343 DNA in lung and colon tumors, does not provide a readily apparent use for the polypeptide or the antibodies against the polypeptide, because the assay does not show that the polypeptide is also amplified in these tumors.

Accordingly, the subject matter defined in claims 45-49 is afforded an effective filing date of 07/11/2001 which is the filing date of the current application.

Claim Rejections under 35 U.S.C. §101/112:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3a. Claims 45-49 are stand rejected under 35 U.S.C. §101, because the claimed invention is not supported by either a specific and substantial asserted utility or a well

established utility, and are also rejected under 35 U.S.C. 112, first paragraph, for reasons of record set forth in the office actions mailed on 21 April 2003 and 14 January 2004. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Response to Applicants' arguments:

4a. Applicant's arguments (submitted with the amendment of 14 July 2004) have been fully considered but are not found to be persuasive for the following reasons. The Ashkenazi and Polakis declarations under 37 CFR 1 .132 filed 07 July 2004 are also insufficient to overcome the rejection of claims 124-126 and 129-131 based upon 35 U.S.C. §101 and 1 12, first paragraph as set forth in the last Office action for the following reasons.

Applicants review the evidentiary standard regarding the legal presumption of utility. Applicant argues that the USPTO has not met its burden of overcoming the presumption of the truth of an asserted utility. This has been fully considered but is not found to be persuasive.

The examiner takes no issue with Applicant's discussion of the evidentiary standard regarding the legal presumption of utility. Furthermore, the rejection does not question the presumption of truth, or credibility, of the asserted utility.

The asserted utilities of cancer diagnostics for the claimed method using antibodies that bind to the polypeptide of SEQ ID NO:263, are credible and specific. However, they are

not substantial. The data set forth in the specification are preliminary at best. As the courts have discussed in Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct, 1966), an asserted utility must exist in currently available form. The specification indicates that the PRO343 gene is amplified in certain cancers. However, the literature reports that gene amplification does not necessarily result in increased expression at the mRNA and polypeptide levels. See Konopka et al., Haynes et al (cited in the previous Office Action).

Applicant urges that the USPTO has not made a prima facie case of lack of utility, in that Konopka et al. is limited to the abl gene, which is not recited in the claims. Applicant takes issue with the conclusion that increased copy number may not result in increased polypeptide expression, urging that the standard is not absolute certainty. Applicant argues that the abl gene may be a discrepancy. Applicant asserts that the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded polypeptide is likely to be expressed at an elevated level.

This argument is fully considered, but is not found persuasive. Konopka et al. is relevant in spite of its being directed to a different gene, since it provides an example of an instance wherein a gene is amplified in a tumor whereas there is no corresponding increase in polypeptide expression. The examiner agrees with Applicant's statement that absolute certainty is not the legal standard for utility. However, once again, the credibility of the assertion of utility is not questioned. The asserted utility is not substantial. The literature evidences that gene amplification does not reliably correlate with increased mRNA or polypeptide expression. Therefore, further research would be

required by the skilled artisan to determine if the disclosed results regarding a gene amplification event in tumors is also reflected at the mRNA and polypeptide levels. The gene amplification data are preliminary with respect to whether or not the antibodies that bind to the encoded polypeptides can be used in diagnosing cancer. Since the asserted utility that antibodies that bind to the PRO343 polypeptide can be used as cancer diagnostics is not in currently available form, the asserted utility is not substantial.

Applicant argues that the Haynes et al. publication does not support the rejection. Applicant characterizes Haynes et al. as teaching that there is a general trend but no strong correlation between polypeptide expression level and transcript level. Applicant criticizes Haynes et al. for being directed to a study of yeast polypeptides. Applicant further characterizes Haynes et al.'s conclusions as showing that there is a positive correlation between transcript and polypeptide for most of the 80 yeast polypeptides studied, but the correlation is not linear and thus one cannot accurately predict polypeptide levels from mRNA levels. Applicant stresses that very few data points scattered away from the expected normal or showed a lack of correlation between mRNA and polypeptide. Applicant concludes that Haynes et al. show that it is more likely than not that a positive correlation exists between mRNA and polypeptide levels.

This has been fully considered but is not found to be persuasive. In the instant case, the specification provides data showing a very small increase in DNA copy number, approximately 2-3-fold, in a few tumor samples for PRO343. There is no evidence regarding whether or not the PRO343 mRNA or polypeptide levels are also

increased in these tumor samples. Since the instant claims are directed to a method of diagnosing lung or colon cancer using antibodies that bind to the PRO343 polypeptide, it was imperative to find evidence in the relevant scientific literature whether or not a small increase in DNA copy number would be considered by the skilled artisan to be predictive of increased in mRNA and polypeptide levels, Konopka et al. was cited as evidence showing lack of correlation between gene amplification and increased polypeptide levels. Haynes et al. was cited as providing evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much as 40 fold or even 50-fold were not uncommon (p. 1863). Haynes et al. used yeast as an art-accepted model for eukaryotic systems. Given how small the DNA copy number of PRO343 increased, and the evidence provided by Haynes et al. and Konopka et al., it was clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or polypeptide levels. One skilled in the ad would do further research to determine whether or not the PRO343 polypeptide levels increased significantly in the tumor samples. Such further research requirements makes it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in Brenner v. Manson, 148 U.S.P.Q.689 (Sup. Ct, 1966), in which the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", '[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification

for permitting an applicant to engross what may prove to be a broad field" and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

4b. Applicant refers to three additional articles (Orntoft et al., Hyman et al. and Pollack et al.) as providing evidence that gene amplification generally results in elevated levels of the encoded polypeptide. Applicant characterizes Orntoft et al. as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fo1d gain of DNA showed a corresponding increase in mRNA transcripts. Applicant characterizes Hyman et al. as providing evidence of a prominent global influence of copy number changes on gene expression levels. Applicant characterizes Pollack et al. as teaching that 62% of highly amplified genes show moderately or highly elevated expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels.

This has been fully considered but is not found to be persuasive. Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region, which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO343 in the instant specification. That is, it is not clear whether or not PRO343 is

in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Orntoft et al. is not clear. Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA over*expression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support utility of the polypeptides of the instant invention. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention. Importantly, none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of potential cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the antibodies that bind to PRO343 polypeptides have utility in the fields of cancer diagnostics are not substantial.

37 CFR 1.132 Declarations:

4c. Applicant presents a declaration by Dr. Polakis filed with the response under 37 CFR 1.132. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately

30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule.

This has been fully considered but is not found to be persuasive. First, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO343 or antibodies binding it in lung or colon cancer samples relevant to normal samples. Only gene amplification data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 45-49 based upon 35 U.S.C. §101 and §112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels, and not gene amplification levels and polypeptide levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean

expression level between breast cancer samples and normal samples in a micoarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10- fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

4d. Applicant argues that even if a prima facie case of lack of utility has been established, it should be withdrawn on consideration of the totality of the evidence. Specifically, Applicant refers to the Ashkenazi declaration filed under 37 CFR § 1.132 with the amendment. The declaration and arguments assert that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment.

This has been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-expression would also be useful; unfortunately, there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not present in currently available form, and is not substantial. Applicant provides evidence in the form of a publication by Hanna et al., attached to the amendment. Applicant urges that the publication evidences that the HER-2/neu gene is over-expressed in breast cancers, and teaches that diagnosis of

breast cancer includes testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Applicant argues that the disclosed assay leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna et al. supports the rejection, in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. For all of these reasons, the rejection claims 45-49 made under 35 U.S.C. §101 and §112 is maintained.

Conclusion:

5. No claims are allowed.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia M Hamud whose telephone number is (571) 272-0884. The examiner can normally be reached on Monday, Thursday-Friday, 6:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information:

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Fozia Hamud
Patent Examiner
Art Unit 1647
29 September 2004

JANET ANDRES
PRIMARY EXAMINER